IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Leo Martis et al.	DOCKET NO.:	P94,1481-B
SERIAL NO.:	08/421,020	GROUP ART UNIT:	1204
FILED:	April 12, 1995	EXAMINER:	R.A. Williams

TITLE: "BIOCHEMICALLY BALANCED PERITONEAL DIALYSIS SOLUTIONS"

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF LEO MARTIS, Ph.D.

S I R:

I, Leo Martis, Ph.D., hereby declare as follows:

1. I am a co-inventor of U.S. Patent Application Serial No. 08/421,020. I earned a Ph.D. in Pharmacology in 1973. I have been a research chemist at Baxter International Inc. since 1974 and have been a research scientist working in the field of peritoneal dialysis solutions since 1978.

2. I have reviewed the Office Action mailed on August 20, 1996 which rejects the claims of Application Serial No. 08/421,020 in light of the Schambye, Zander and Veech references. I have reviewed the Schambye and Zander references thoroughly and make the following statements as a person skilled in the art of peritoneal dialysis.

3. The Schambye article is allegedly directed toward the optimization of peritoneal dialysis solutions with respect to their effect on normal human polymorphonuclear granulocytes *in vitro*. The Schambye article and the solutions disclosed in the article are not designed or intended to correct metabolic acidosis associated with end stage renal disease. Because Schambye allegedly discloses a solution with a pH of 7.0-7.2 and with a carbonate and lactate concentration of 20 mM and 12.5 mM respectively with no carbon dioxide partial pressure, Schambye does not suggest a composition with the buffer qualities or the ability to maintain the acid-base balance in a patient that is achieved by the example shown at Example 1 at pages 9-10 of the present application. Further,

because Schambye does not suggest using a partial pressure of carbon dioxide.

4. I have also thoroughly reviewed the Zander reference. In the discussion of the "preliminary research" at column 2, line 35-43, Zander discloses a dialysis solution having a pH value of 7.4 +/- 0.5 with a bicarbonate concentration of 24 mmole/l and a carbon dioxide partial pressure of 40 mmHg. However, because this specific combination lacks a weak acid, one skilled in the art would readily recognize the solution disclosed at column 2 of the Zander reference would not be effective in maintaining the acid-base balance in peritoneal dialysis patients. While the Zander preliminary solution may prevent the loss of bicarbonate from the body, it would be deficient in terms of neutralizing the hydrogen ions generated endogenously by the dialysis patient as a result of protein metabolism.

5. Zander allegedly discloses another dialysis solution at column 6, lines 47-53 which is a combination of an acid-containing solution and a base-containing solution. This combination solution has a pH of 7.4, a bicarbonate concentration of 24.0 mmole/l and an acetate concentration of 27.2 mmole/l. However, this proposed solution is unable to maintain the acid-base balance in dialysis patients because the concentration of the weak acid (acetic acid) is too high.

6. Further, it has long been known that acetate damages the peritoneal membrane causing loss of ultrafiltration, see Faller and Marichal, "Loss of Ultrafiltration in Continue Ambulatory Peritoneal Dialysis: A Role for Acetate", *Peritoneal Dialysis Bulletin*, Jan.-Mar. 1984. In any event, if another weak acid was substituted for acetic acid, the concentration would still be too high which would result in a solution unable to maintain the acid-base balance in a peritoneal dialysis patient. As a result, the Zander patent is not credible and the solutions disclosed in the

Zander patent suggest that no thought has been given to the buffer content required to maintain the acid-base balance.

7. In contrast, the unique combination of the buffers and their concentrations of the present invention result in a peritoneal dialysis solution, as exemplified by Example 1 of the present application, that maintains the acid-base balance in a peritoneal dialysis patient suffering from end stage renal disease. The efficacy and safety of the solutions of the present invention have been proven in a clinical study.

8. Specifically, a clinical study was performed with the solution described in Example 1 of the present application. Twelve continuous ambulatory patients used the solution daily for eight weeks. Mean serum bicarbonate levels for the twelve patients were as follows:

	Concentration (mEq/L)
Day 0	25.3 +/- 3.4
Week 4	26.5 +/- 3.8
Week 8	26.6 +/- 3.4

Thus, the mean serum bicarbonate levels for the twelve patients during the eight week treatment period was within the normal range of 24-32 mEq/L.

9. The biocompatibility of the solution described in Example 1 of the present application was compared with that of currently used solutions in clinical practice, specifically the solution sold under the DIANEAL trademark. The following table shows the effect of a 30 minute exposure on human peripheral blood polymorphonuclear leukocyte viability (ATP content) and function (phagocytosis):

	% of Control (M199 media plus 0.1%FCS)	
	ATP content	Phagocytosis
DIANEAL	48.0 +/- 22.2	17.3 +/- 10.2
Example 1	111.4 +/- 40.4	48.6 +/- 19.3

A comparison of the solution of Example 1 and the DIANEAL solution is as follows:

	Example 1	DIANEAL
Dextrose (gm/dl)	1.5	1.5
Sodium (mEq/L)	132	132
Chloride (mEq/L)	96	96
Calcium (mEq/L)	3.5	3.5
Magnesium (mEq/L)	0.5	0.5
Lactate (mEq/L)	15.0	40.0
Bicarbonate (mEq/L)	25.0	____

10. The above results suggest that a unique combination of bicarbonate, lactate, and carbon dioxide partial pressure as described in the present invention and exemplified by Example 1 of the present application is essential to both maintain the acid-base balance of dialysis patients and further to improve biocompatibility.

11. As one skilled in the art, I can state that neither the solutions disclosed in Schambye nor the solutions disclosed in Zander, nor any combination thereof, can provide a dialysis solution that can maintain the acid-base balance of a dialysis patient. Further, Zander does not address the need for improved biocompatibility of peritoneal dialysis solutions and therefore no combination of Schambye and Zander provides a peritoneal dialysis solution that both maintains an acid-base balance in a peritoneal dialysis patient and also provides improved biocompatibility.

I hereby declare that all statements made herein are of my own knowledge and are true and that all statements made on information and belief are believed to be true. I also make this declaration with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001) and further that any such willful false statements and the like may jeopardize the validity of this application or any patent issuing thereon.

Date: 12-13-96

Leo Martis

Leo Martis, Ph.D.